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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. |
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| 09/044,696 | 03/18/98 | BARCHFELD G | 1393.002 |

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| EXAMINER | |
|---|---|
| DEVI,S | |
| **ART UNIT** | **PAPER NUMBER** |
| 1641 | 15 |

**DATE MAILED:** 04/25/00

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

| Application No. | Applicant(s) |
|---|---|
| 09/044,696 | Barchfeld et al. |
| **Examiner** | **Group Art Unit** |
| S. Devi, Ph.D. | 1641 |

☒ Responsive to communication(s) filed on *12/06/99.*

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

**Disposition of Claims**

☒ Claim(s) *1-19 and 21-30* ~~is~~/are pending in the application.

Of the above, claim(s) *1-18* ~~is~~/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *19 and 21-30* ~~is~~/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

**Application Papers**

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

*--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---*

## DETAILED ACTION

### Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 12/06/99 (paper no. 13) in response to the non-final action mailed 08/04/99 (paper no. 10), which amendment has been entered.

### Associate Power of Attorney

2) Acknowledgment is made of Applicants' notice of the Associate Power of Attorney filed 12/06/99 (paper no. 14).

### Status of Claims

3) Claims 1-30 are pending in this application.

Claim 20 has been canceled via the amendment filed 12/06/99 (paper no. 13).

Claims 19 and 21-30 are under examination.

### Objection Maintained

4) The objection to the drawings made under 37 C.F.R 1.84 in paragraph 7 of the Office Action mailed 08/04/99 (paper no. 10) is maintained for reasons set forth therein. Applicants assure the Office that 37 C.F.R 1.84 would be complied upon indication of allowed claims.

### Objection Withdrawn

5) The objection to the oath or declaration made in paragraph 8 of the Office Action mailed 08/04/99 (paper no. 10) as being defective is withdrawn as indicated to the Applicants via a telephone message left on 13 September 1999. The late-matched oath or declaration is in compliance.

### Rejections Moot

6) The rejection of claim 20 made in paragraph 10(e) of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. 112, second paragraph, as being indefinite, is moot in light of Applicants' cancellation of the claim.

7) The rejection of claim 20 made in paragraph 12 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. § 102(b) as being anticipated by Tommaso *et al.* (*Infect. Immun.* 64: 974-979, 27 February 1996) is moot in light of Applicants' cancellation of the claim.

**8)** The rejection of claim 20 made in paragraph 13 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. § 102(b) as being anticipated by Douce *et al.* (*PNAS* 92:1644-1648, February 1995) is moot in light of Applicants' cancellation of the claim.

**9)** The rejection of claim 20 made in paragraph 14 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. § 102(b) as being anticipated by Rappuoli *et al.* (WO 95/17211, published 06/29/95) (WO '211) is moot in light of Applicants' cancellation of the claim.

**10)** The rejection of claim 20 made in paragraph 15 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. § 102(b) as being anticipated by Gajewzyk *et al.* (WO 95/34323, published 21 December 1995) is moot in light of Applicants' cancellation of the claim.

**11)** The rejection of claim 20 made in paragraph 16 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. § 102(a) as being anticipated by Pizza *et al.* (WO 97/02348, published 23 January 1997) (Pizza *et al.*, WO '348) is moot in light of Applicants' cancellation of the claim.

**Rejections Withdrawn**

**12)** The rejection of claims 21 and 25 made in paragraphs 10(a) and 10(b) of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendments to the claims.

**13)** The rejection of claims 19, 21-23 and 30 made in paragraph 12 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. § 102(b) as being anticipated by Tommaso *et al.* (*Infect. Immun.* 64: 974-979, 27 February 1996) is withdrawn in light of Applicants' exclusion of vaginal route as a parenteral route of administration in the specification.

**14)** The rejection of claims 19, 21-22, 25, 26 and 28-30 made in paragraph 15 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. § 102(b) as being anticipated by Gajewzyk *et al.* (WO 95/34323, published 21 December 1995) is withdrawn in light of Applicants' amendments to one or more claims.

**15)** The rejection of claims 19, 21, 25, 26 and 30 are rejected under 35 U.S.C § 102(b) as being anticipated by Douce *et al.* (*PNAS* 92:1644-1648, February 1995) is withdrawn in light of Applicants' arguments.

**16)** The rejection of claims 19, 21 and 25-30 are rejected under 35 U.S.C § 102(b) as being anticipated by Rappuoli *et al.* (WO 95/17211, published 06/29/95 -Applicants' IDS) (WO '211) is withdrawn in light of Applicants' arguments.

**Rejections Maintained**

**17)** The rejection of claim 22 made in paragraph 9 of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. 112, first paragraph, is maintained for reasons set forth therein and those that are set forth below. Applicants are asked to note that claims 19, 21 and 24-30 are now included under this scope and/or lack of enablement rejection.

Applicants direct the Office's attention to Example 5 in the specification and contend that mice used in this experiment survived upto 80 days, thus contrasting the cited reference of Pizza *et al.* Applicants state that LT-R72 is indeed "detoxified". Further, Applicants submit WO 98/18928 patent (Exhibit A), published after the filing date of the instant application, and state that the patent (see 5 of Applicants response filed 12/06/99):

> ...demonstrates that LT-R72 is **indeed detoxified**. In particular, Figures 4 and 5 show *in vitro* and *in vivo* toxicity experiments, respectively, and show that **LT-R92 is non-toxic**. [Emphasis added.]

With regard to CT-S109, Applicants contend that Pizza *et al.* is silent as to any substitutions at position 109 of CT and therefore does not provide evidence that this mutant is toxic. Applicants further assert that the specification teaches how to make and use the mutant, methods of testing mutants for toxicity and therefore CT-S109 is adequately enabled.

Applicants' arguments have been carefully considered, but are not found to be persuasive. The instant claim, prior to the amendment, included the limitation of "the detoxified mutant", "LT-K63, LT-R72" or "CT-S109". As amended, the claim includes CT-S109 as a detoxified parenteral adjuvant. As clearly set forth in paragraph 9 of the Office Action mailed 08/04/99 (paper no. 10), the art reflects considerable unpredictatbility with regard to the toxicity of LT mutants. For instance, with regard to LT-R72 mutant, the state of the art suggests that an LT mutant having a site directed substitution of Alanine to Arginine at position 72 is not "detoxified". For instance, Pizza *et al.* (*Mol. Microbiol.* 14: 51-60, October 1994) teach such a mutant. See Table 1, Fig 1k and page 57, left column, last paragraph. Table 1 illustrates that the mutant named "R72" having a Ala->Arg sub A mutation remains toxic (toxicity is rated as ++). Pizza *et*

*al.* state that this mutant was "fully toxic" as in the case of the mutant having a substitution at Ser-68 (see page 57, left column, last paragraph). Contrary to the Applicants' assertion, Example 5 of the instant application does **not** provide any data reflective of the "detoxified" nature of LT-R72 mutant.

With regard to Applicants Exhibit A, a review of WO 98/18928 patent indicates just the opposite of what Applicants assert. Figures 4 and 5 of Exhibit A clearly show that LT-R72 mutant is **not** "detoxified", while LT-K63 is. Furthermore, Exhibit A on page 44, lines 16-21, explicitly states that LT-A72R was "less toxic" whereas LTK63 was "completely non-toxic".

With regard to the mutant CT-S109, although the reference of Pizza *et al.* (*Mol. Microbiol.* 14: 51-60, October 1994) is silent about the substitution at position 109, it reflects unpredictability in the state of the art at the time, as to which of the site directed substitutions at specific positions would eliminate toxicity while at the same time retain structural and functional integrity of proteins such that it acts as an effective parenteral adjuvant. The instant specification lacks evidence that a CT mutant comprising a substitution of serine at position 109 (CT-S109) is indeed "detoxified" and functional as an adjuvant when administered by any parenteral route. This is critical because Pizza *et al.* (1994) have shown that replacement at multiple positions, for example, at His-70, Val-60, Ala-45 and Leu-41, in *E. coli* LT-A resulted in the "collapse of the protein structures" and altered "the structural assembly" (see page 54, last two lines, and page 57) of the proteins. Pizza *et al.* (1994) have shown that amino acid substitutions resulting in mutant proteins, M59, H72 and N192 remained as toxic (+++) as the wild type toxin (see Table 1). A similar negative observation is possible with CT-S109 absent a showing of parenteral adjuvanticity and absence of toxicity. Therefore, without adequate evidence and/or guidance, there is no certainty that any substitutions at position 109 of CT would yield a "detoxified" mutant that is effective as a parenteral adjuvant. The Office has clearly met the burden of undue experimentation due to the lack of specific evidence and/or guidance, the lack of working examples enabling detoxified and functional (as parenteral adjuvants) mutant species, LT-R72 and CT-S109, the breadth of the claim, the demonstrated unpredictability as reflected in the state of the art, and the quantity of experimentation necessary.

Applicants are asked to limit the scope of the claims to methods using mutant species that

are fully enabled as "detoxified" and "parenteral" adjuvants, or provide post-filing evidence enabling the claimed method using mutant species that are currently non-enabled.

**18)** The rejection of claim 27 made in paragraph 10(c) of the Office Action mailed 08/04/99 (paper no. 10) under 35 U.S.C. 112, second paragraph, as being indefinite, is maintained for reasons set forth therein.

**19)** The rejection of claims 19, 21-23 and 25-30 made in paragraph 16 of the Office Action mailed 08/04/99 (paper no. 10) are rejected under 35 U.S.C § 102(a) as being anticipated by Pizza *et al.* (WO 97/02348, published 23 January 1997 -Applicants' IDS) (Pizza *et al.*, WO '348) is maintained for reasons set forth therein and those that are set forth below.

Applicants contend that Pizza's teaching that LT or CT mutants act as parenteral adjuvants is unsubstantiated general statements and therefore Pizza's disclosure does not enable the claimed methods.

Applicants' arguments have been carefully considered, but are not found to be persuasive. As set forth in paragraph 16 of the Office Action mailed 08/04/99, Pizza *et al.* disclose a method of immunizing a vertebrate subject by administering an immunologically effective amount or dose of a composition comprising a detoxified mutant protein of a bacterial toxin such as cholera toxin subunit A (CT-A) or *E. coli* heat-labile toxin subunit A (LT-A), (i.e. ADP-ribosylating toxins) comprising serine at position 63 and Arginine at position 192 replaced with another amino acid, a pharmaceutically acceptable carrier and a second immunogenic toxin antigen (see claims 11, 4, 2 and 1; page 15, lines 33-36, and page 16, lines 18 and 19). The pharmaceutically acceptable carriers or vehicles may be water, saline, glycerol or ethanol (see page 16, lines 1-5). The immunogenic detoxified protein acts as an adjuvant for the second immunogenic protein or antigen, administered separately, sequentially or along with the immunogenic detoxified protein (see page 9, lines 1, 2 and 9-13). One of the detoxified mutant protein used is LTK63 (see page 11). CTK63/G192, a detoxified mutant protein derived from CT is also disclosed (see page 46). The composition may be conventionally administered **parenterally**, i.e. subcutaneously or intramuscularly, or may be administered transdermally, i.e. transcutaneously (see page 16, last paragraph). Thus, Pizza *et al.* expressly disclosed the claimed method.

It is noted in this context that Applicants' specification is similarly limited to general statements at least as far as the use of detoxified CT-S109 mutant in the claimed method is concerned. Yet Applicants claim that their method is enabled. Pizza *et al.* have expressly disclosed the claimed method prior to the filing date of the claimed invention. Via the instant disclosure, Applicants have obtained successful results based on Pizza's teachings.

**New Rejections**

Applicants are asked to note the new rejections made in this Office Action, which was partly necessitated by Applicants' amendments to the claims.

**Rejections under 35 U.S.C. § 112, First Paragraph**

**20)** Claims 19, 21 and 24-30 are rejected under 35 U.S.C. 112, first paragraph, as being non-enabled. Please see paragraph 17 above for the basis of the rejection.

**21)** Claims 19, 21, 25, 26 and 30 are rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method for immunizing a vertebrate subject comprising intramuscularly or subcutaneously (parenterally) administering an effective amount of the specific detoxified bacterial ADP-ribosylating toxin mutant adjuvant, LT-K63, or transcutaneously administering an effective amount of the specific bacterial ADP-ribosylating toxin mutant adjuvant, LT-R72, and at least one selected antigen, does not reasonably provide enablement for such a method using any other mutants, detoxified or less toxic (including CT-S109 mutant), that act as adjuvants by any parenteral routes. For example, Examples 1-4 enable the claimed method using the specific detoxified mutant LT-K63 as an adjuvant when administered by two different parenteral routes, intramuscular and subcutaneous. Example 5 enables the claimed method using the less toxic mutant LT-R72 as an adjuvant when administered only by trancutaneous route. Thus, the entire breadth of instant claims are not enabled and the claims do not meet the enablement provision of 35 U.S.C. § 112, first paragraph, for the following reasons.

Many of the factors regarding undue experimentation have been summarized in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Circ. 1988) as follows:

The quantity of experimentation necessary (time and expense);
- The amount of direction or guidance presented;

- The presence or absence of working examples of the invention;
- The nature of the invention;
- The state of the art;
- The relative skill of those in the art;
- The predictability or unpredictability of the art; and
- The breadth of the claims.

In the instant case, the state of the art reflects uncertainty. For example, as admitted by Applicants and as reflected in the state of the art, not all LT mutants act as effective adjuvants when administered by any parenteral route. For example, Applicants themselves state in page 6 of their response filed 12/06/99 (paper no. 13) that with regard to the subcutaneous (i.e., parenteral administration currently encompassed by the Applicants' definition) immunization method, the mutant LT toxins of prior art (for example, LTK7 mutant) (Douce *et al. PNAS* 92:1644-1648, February 1995, see Figure 2, and Rappuoli *et al.* - WO 95/17211, see Figure 1), when administered subcutaneously with a selected antigen "produce similar immune responses". Applicants state that "Douce and Rappuoli fail to teach that parenterally-administered detoxified CT, LT and PT mutants act as adjuvants". Thus, by Applicants' own admission and by what is established in the state of the art, it is apparent that a method of immunizing a vertebrate by the broadly recited "parenteral" administration of any LT or CT mutant, detoxified or less toxic, is not enabled. With regard to the mutant CT-S109, no method of immunization by administration via any parenteral route is enabled in the instant specification establishing CT-S109 mutant to be an effective detoxified parenteral adjuvant. The entire scope of instant claims is non-enabled under the provisions of 35 U.S.C. § 112, first paragraph, in view of the demonstrated unpredictability as reflected in the state of the art and the quantity of experimentation necessary.

**Remarks**

**22)** Claims 19 and 21-30 stand rejected.

**23)** Papers related to this application may be submitted to Group 1600, AU 1641 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242.

**24)** Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. The Examiner can normally be reached on Monday to Friday from 8.00 a.m to 4.00 p.m. A message may be left on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for this Group is (703) 305-7939.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

SD
S. Devi
Patent Examiner
April 2000

James C. Housel 4/24/00

JAMES C. HOUSEL
SUPERVISORY PATENT EXAMINER